

ANTI-INFECTIVE BIARYL COMPOUNDS

CROSS-REFERENCES TO RELATED APPLICATIONS

- [0001] This application claims the benefit of US Provisional Application Serial No. 5 60/421,438, filed October 25, 2002, the content which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

- [0002] This invention relates to aromatic compounds having antibacterial activity and 10 methods for their synthesis and use.

DESCRIPTION OF RELATED ART

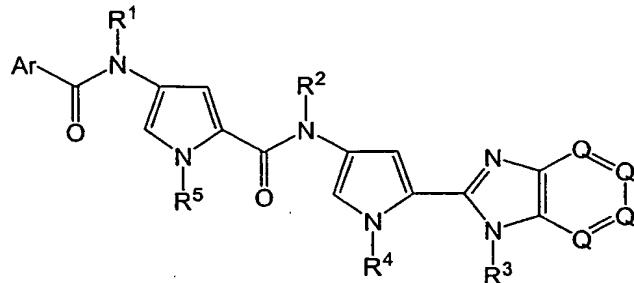
- [0003] The discovery of penicillin and other antimicrobials in the early and mid-20th century generated a period of optimism about the medical profession's ability to treat microbial infections. However, the evolution of drug-resistant microbe strains - with new 15 ones being constantly discovered has led to an appreciation of the continuing need to develop new antimicrobials, preferably ones that are structurally different from extant ones or employ a different mechanism of action.

- [0004] Exemplary recent disclosures of new antibacterial compounds include Ge et al., WO 01/74898 (2001); Baird et al., U.S. Application No. 10/132887, filed Apr. 24, 2002; Bürli et 20 al., U.S. Application No. 10/165856, filed Jun. 6, 2002; McMinn et al., U.S. Application No. 10/165433, filed Jun. 6, 2002 ("McMinn '433"); Bürli et al., U.S. Application No. 10/165857, filed Jun. 6, 2002; Bürli et al., U.S. Application No. 10/165764, filed Jun. 6, 2002; and Bürli et al., U.S. Provisional Application no. 60/400671, filed Aug. 2, 2002. Matsunaga et al., U.S. 25 5,808,087 (1998), U.S. 5,821,258 (1998), U.S. 5,852,011 (1998) ("Matsunaga '011"); JP 11-171886; and JP 11-89594 also disclose compounds reportedly having antimicrobial activity.

- [0005] Especially noteworthy are McMinn '433 and Matsunaga '011, each of which discloses as anti-microbial agents pyrrole-benzimidazole compounds characterized by a carboxy amide $(-(C=O)NH-)$ or carboxy ester $(-(C=O)O-)$ group attached to the 6-member ring of the benzimidazole ring system.

BRIEF SUMMARY OF THE INVENTION

[0006] The present invention provides novel biaryl antiinfective compounds, in which a pyrrole ring is directly bonded to a 6,5-condensed ring system, which can be but is not necessarily a benzimidazole system. Thus, this invention provides a compound according to
5 formula (1)



(I)

and the solvates, prodrugs, and pharmaceutically acceptable salts thereof, wherein

[0007] Ar is an unsubstituted or substituted phenyl group, 5-member heteroaryl group, 6-

10 member heteroaryl group, 6,6-condensed ring aryl or heteroaryl group, or 6,5-condensed ring heteroaryl group;

[0008] each Q is independently N, CH, C(R⁶), where R⁶ is as defined hereinbelow, with the proviso that no more than two Q's are N;

[0009] each of R¹, R², R³, and R⁴ independently is H or a (C₁-C₅) alkyl group;

15 [0010] each R⁵ is independently H, a substituted or unsubstituted (C₁-C₁₂) alkyl group, or a substituted or unsubstituted (C₁-C₁₂)heteroalkyl group; and

[0011] each R⁶ is independently a substituted or unsubstituted (C₁-C₁₂) alkyl, OR⁵, N(R⁵)₂, O(CO)R⁵, N(CO)R⁵, Cl, F, or Br.

BRIEF DESCRIPTION OF THE DRAWINGS.

[0012] Figs. 1-26 show chemical reactions used to make compounds of this invention.

DETAILED DESCRIPTION OF THE INVENTION

Abbreviations and Definitions

5 [0013] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.* C₁-C₁₀ means one to ten carbons). Examples of saturated hydrocarbon radicals include groups such as methyl, ethyl,
10 n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl,
15 3-butynyl, and the higher homologs and isomers.

[0014] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by -CH₂CH₂CH₂CH₂- . Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is
20 a shorter chain alkyl or alkylene group, generally having six or fewer carbon atoms.

[0015] The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively.

[0016] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be a heteroatom(s) O, N and S may be placed at any interior position of the
25 heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group,
30

including the position at which the alkyl group is attached to the remainder of the molecule. Examples include -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, Si(CH₃)₃, -CH₂-CH=N-OCH₃, and -CH=CH-N(CH₃)-CH₃. Up to two heteroatoms may be consecutive, such 5 as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₃. Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by -CH₂-CH₂-S-CH₂CH₂- and -CH₂-S-CH₂-CH₂-NH-CH₂-.

For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and 10 heteroalkylene linking groups, no orientation of the linking group is implied.

[0017] The terms "Cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of 15 cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetralydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

20 [0018] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C₁-C₄) alkyl" is meant to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

25 [0019] The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from zero to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are 30 optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-

imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

- [0020] For brevity, the term "aryl" when used in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above.
- 10 Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (*e.g.*, a methylene group) has been replaced by, for example, an oxygen atom (*e.g.*, phenoxyethyl, 2-pyridyloxymethyl, 3-(1-naphthoxy)propyl, and the like). Each of the above terms (*e.g.*, "alkyl," heteroalkyl," "aryl" and "heteroaryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

- [0021] Substituents for the alkyl, heteroalkyl, aryl, and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be a variety of groups selected from: -OR', =O, =NR', -N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', -CO₂R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR'R', -NR-C(O)₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R", -CN and -NO₂ in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R" and R''' each independently refer to 20 hydrogen, unsubstituted (C₁-C₈) alkyl and heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, or aryl-(C₁-C₄) alkyl groups. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R" is meant to include 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of 25 skill in the art will understand that the term "alkyl" is meant to include groups such as halo-alkyl (*e.g.*, -CF₃ and -CH₂CF₃) and acyl (*e.g.*, -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like). Preferably, the substituted alkyl and heteroalkyl groups have from 1 to 4 substituents, more preferably 1, 2 or 3 substituents. Exceptions are those perhalo alkyl groups (*e.g.*,

pentafluoroethyl and the like) which are also preferred and contemplated by the present invention.

[0022] Similarly, substituents for the aryl and heteroaryl groups are varied and are selected from: -halogen, -OR', -OC(O)R', -NR'R'', -SR', -R', -CN, -NO₂, -CO₂R', -CONR'R'', -C(O)R', -OC(O)NR'R'', -NR"C(O)R', -NR"C(O)₂R', -NR'-C(O)NR'R''', -S(O)₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂NR'R'', -N₃, -CH(Ph)₂, perfluoro(C₁-C₄)alkoxy, and perfluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'' and R''' are independently selected from hydrogen, (C₁-C₄)alkyl and heteroalkyl, unsubstituted aryl and heteroaryl, (unsubstituted aryl)-(C₁-C₄)alkyl, and (unsubstituted aryl)oxy-(C₁-C₄)alkyl.

[0023] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CH₂)_q-U-, wherein T and U are independently -NH-, -O-, -CH₂- or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may 15 optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CH₂-,-O-, -NH-, -S-, -S(O)-, -S(O)₂-,-S(O)₂NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the 20 aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -(CH₂)_s-X-(CH₂)_t, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-,-S(O)₂NR'-. The substituent R' in -NR'- and -S(O)₂NR'- is selected from hydrogen or unsubstituted (C₁-C₆)alkyl.

[0024] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

[0025] The term "pharmaceutically acceptable salts" is meant to include salts of the active 25 compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic 30

functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic,

5 monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, ascorbic, propionic, isobulyric, malcic, malonic, lactic, malic, glutamic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic,

10 lactobionic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid

15 addition salts.

[0026] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the

20 compound for the purposes of the present invention.

[0027] In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present

25 invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0028] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to

30 unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or

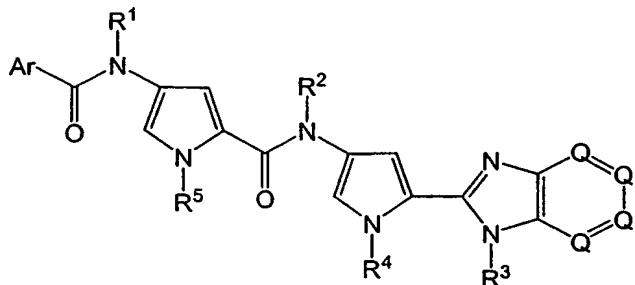
amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0029] Certain compounds of the present invention possess asymmetric carbon atoms (chiral centers) or double bonds; the racemates, diastereomers, geometric isomers and 5 individual isomers are all intended to be encompassed within the scope of the present invention.

[0030] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium 10 (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

Compounds

[0031] The present invention provides novel biaryl antiinfective compounds, in which a 15 pyrrole ring is directly bonded to a 6,5-condensed ring system. An exemplary 6,5-condensed ring system is a benzimidazole system. Thus, this invention provides a compound according to formula (I)



(I)

20 and the solvates, prodrugs, and pharmaceutically acceptable salts thereof, wherein

[0032] Ar is an unsubstituted or substituted phenyl group, 5-member heteroaryl group, 6-member heteroaryl group, 6,6-condensed ring aryl or heteraryl group, or 6,5-condensed ring heteroaryl group;

[0033] each Q is independently N, CH, C(R^6), where R^6 is as defined hereinbelow, with the 25 proviso that no more than two Q's are N;

[0034] each of R¹, R², R³, and R⁴ independently is H or a (C₁-C₅) alkyl group;

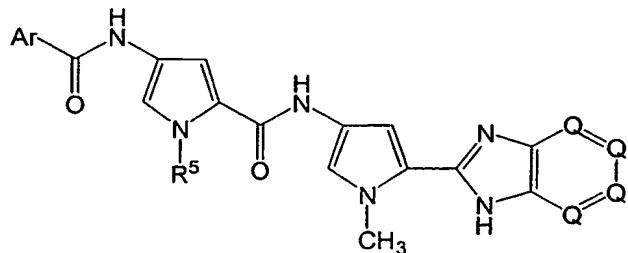
[0035] each R⁵ is independently H, a substituted or unsubstituted (C₁-C₁₂)alkyl group, or a substituted or unsubstituted (C₁-C₁₂) heteroalkyl group; and

[0036] each R⁶ is independently a substituted or unsubstituted (C₁-C₁₂)alkyl, OR⁵, N(R⁵)₂,

5 O(CO)R⁵, N(CO)R⁵, Cl, F, or Br.

[0037] Exemplary suitable R¹, R², R³, and R⁴ are H, methyl, ethyl, propyl, n-propyl, isopropyl, butyl, isobutyl, 2-butyl, t-butyl, n-propyl, 2-propyl, and 3-propyl. Preferably, R¹, R², R³, and R⁴ are H or methyl, with H being especially preferred in the instance of R¹, R², and R³ and methyl being especially preferred in the instance of R⁴.

10 [0038] In one group of preferred embodiments, R¹, R², and R³ are each H and R⁴ is methyl, i.e., as represented by formula (II)



(II)

where Q and R⁵ are as previously defined.

15 [0039] Ar can be an unsubstituted or substituted

(a) phenyl group;

(b) 5-member heteroaryl group, such as an imidazolyl, pyrrolyl, pyrazolyl, furanyl, isothiazolyl, oxazolyl, isoxazolyl, thiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, or thieryl group;

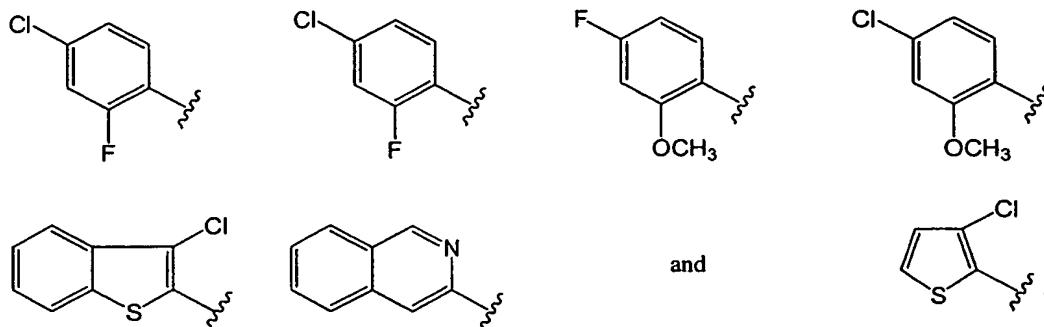
(c) 6-member heteroaryl group, such as a pyridyl, pyrimidyl, pyraeinyl pyridazinyl, or triazinyl group;

(d) 6,6-condensed ring aryl or heteroaryl group, such as a naphthyl, quinolyl or isoquinolyl group; or

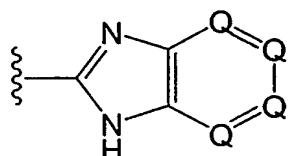
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(e) 6,5-condensed ring heteroaryl group, such as a benzothienyl, indolyl, or benzofuranyl group.

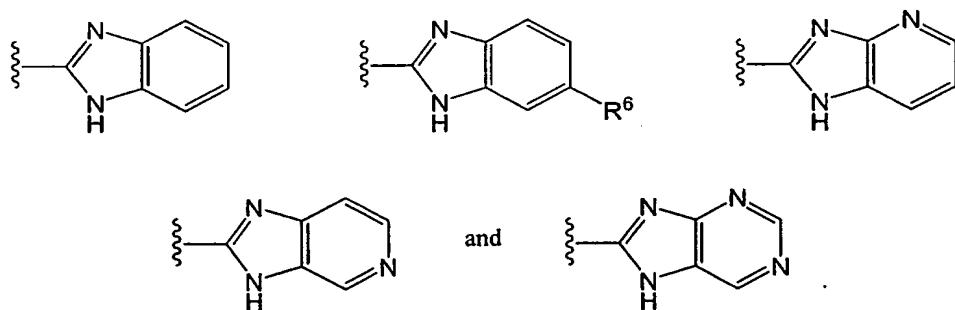
[0040] Preferably Ar is selected from the group consisting of



5 [0041] Preferred embodiments of the 6,5-condensed ring system

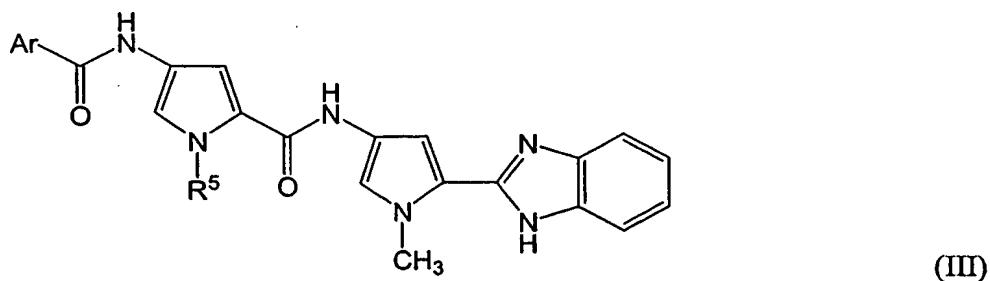


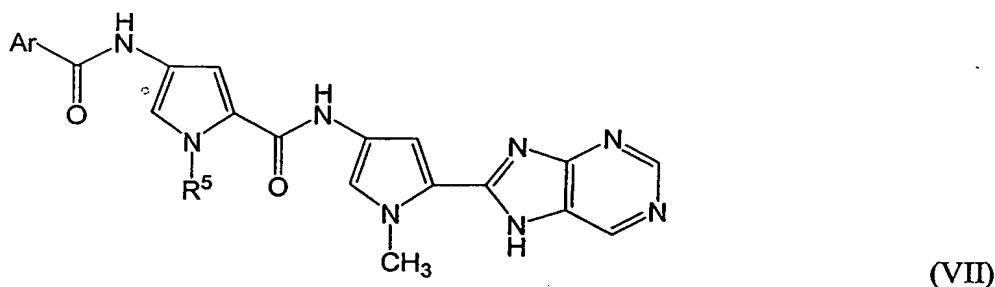
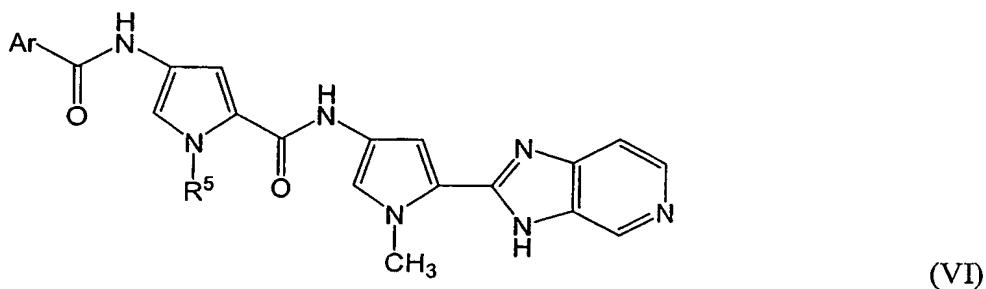
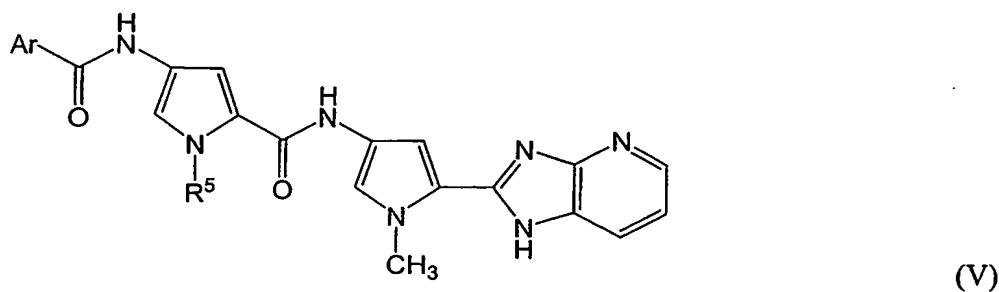
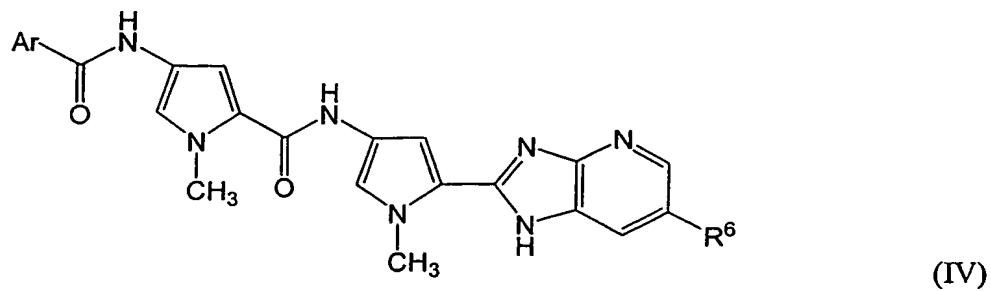
in compounds of formulae (I) and (II), include:



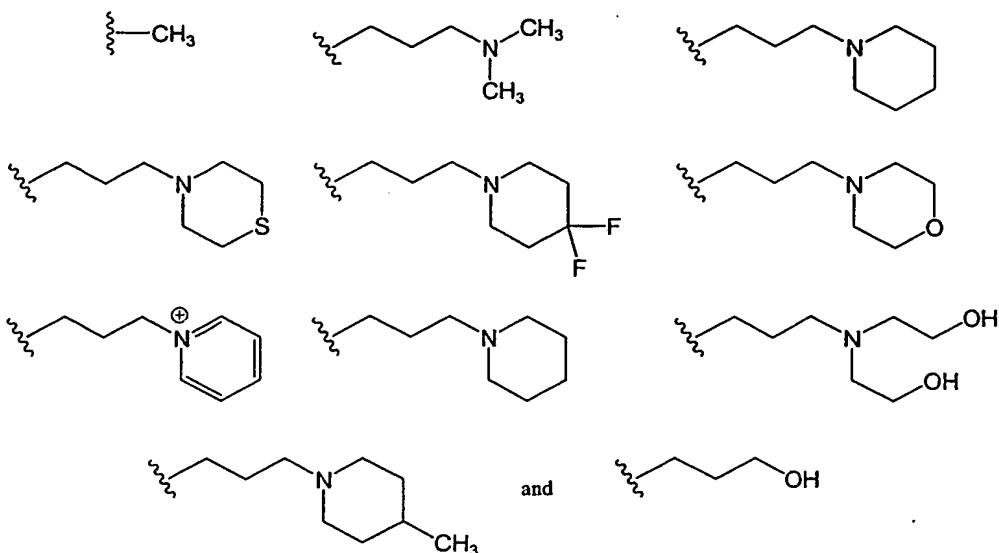
[0042] In a preferred embodiment, at least one Q is N.

10 [0043] Combinations of the foregoing condensed 6,5 ring systems in preferred embodiments of compound I are represented in formulae (III) through (VII), where Ar, R⁵, and R⁶ are as previously defined:

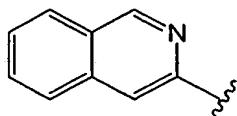




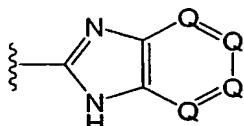
5 [0044] R^5 preferably is a lower alkyl group such as methyl (especially), ethyl, propyl or isopropyl, $(CH_2)_n(Am)$, or $(CH_2)_n(OH)$, where n is 2, 3, 4, or 5 (especially 3) and Am is an alkyl amine group or a quaternary ammonium group. Examples of preferred R^5 's include:



[0045] In a preferred embodiment of compound (I), R⁵ is methyl, Ar is



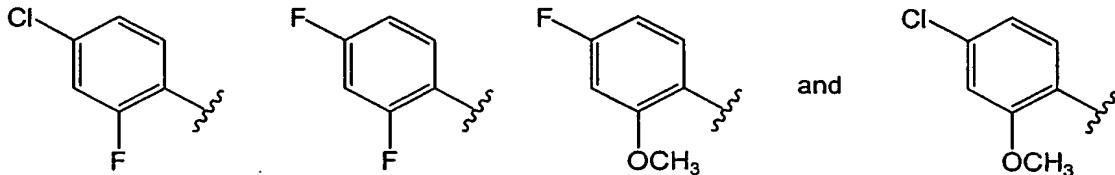
and in the condensed 6,5 ring system



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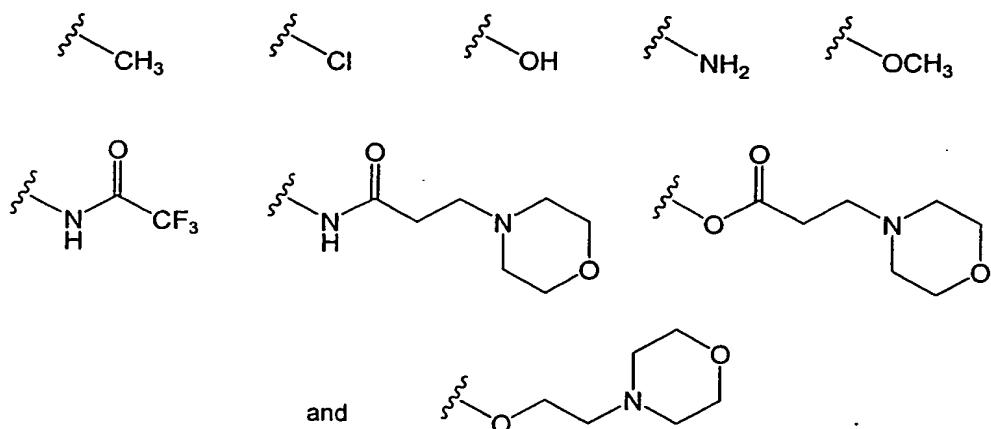
at least one Q is N and the remaining Q's are CH.

[0046] In another preferred embodiment of compound (I), Ar is selected from the group consisting of



10 and R⁵ is (CH₂)₃N(CH₃)₂.

[0047] R⁶ preferably is a lower alkyl group such as methyl (especially), ethyl, propyl or isopropyl, OR⁵, NH(CO)R⁵, O(CO)R⁵, N(R⁵), or Cl. Examples of preferred R⁶'s include:



[0048] Exemplary specific compounds (I) are listed in Table A (wherein each R¹, R², and R³ is H and each R⁴ is methyl).

Table A
Exemplary Compounds (I)

Ref. No.	Ar	R ⁵	Compound (I)
A-1			
A-2	Same		
A-3	Same	Same	
A-4	Same	Same	
A-5	Same	Same	
A-6	Same	Same	
A-7	Same	Same	
A-8	Same	Same	

Table A
Exemplary Compounds (I)
(cont'd)

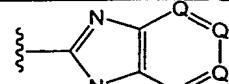
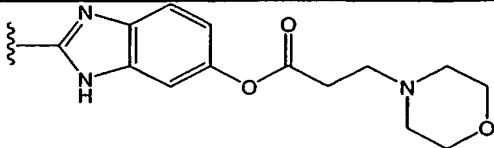
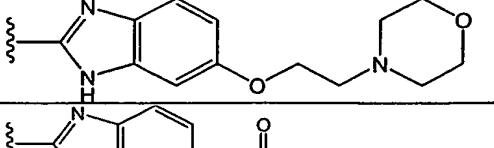
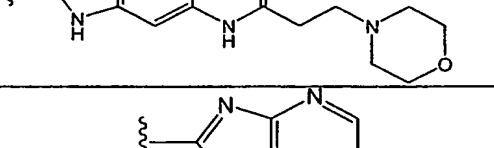
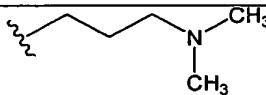
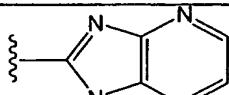
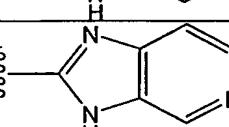
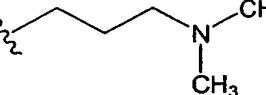
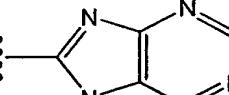
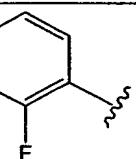
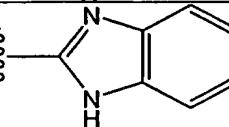
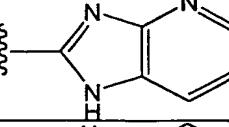
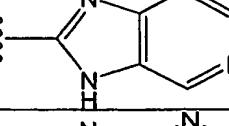
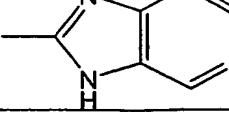
Ref. No.	$\text{Ar}-\text{\zeta}$	$\text{\zeta}-\text{R}^5$	
A-9	Same	Same	
A-10	Same	$\text{\zeta}-\text{CH}_3$	
A-11	Same	Same	
A-12	Same		
A-13	Same	Same	
A-14	Same	$\text{\zeta}-\text{CH}_3$	Same
A-15	Same		
A-16		Same	
A-17	Same	Same	
A-18	Same	Same	
A-19	Same	Same	

Table A (continued)

Ref. No.	Ar—	—R ⁵	—Q—Q
A-20			
A-21		Same	Same
A-22		Same	Same
A-23	Same		Same
A-24	Same		Same
A-25	Same		Same
A-26	Same		Same
A-27	Same		Same
A-28	Same		
A-29	Same	Same	

Table A (continued)

Ref. No.	Ar	R ⁵	
A-30			
A-31		Same	
A-32	Same		Same
A-33	Same		Same
A-34	Same		Same
A-35	Same		Same
A-36	Same		Same
A-37	Same		Same
A-38	Same		Same
A-39	Same		
A-40	Same		Same

Table A (continued)

Ref. No.	Ar— 	 —R ⁵	
A-41			
A-42	Same		Same
A-43	Same		Same
A-44	Same		Same
A-45	Same		
A-46	Same	Same	
A-47		Same	
A-48	Same		Same
A-49	Same		Same
A-50	Same		Same

Table A (continued)

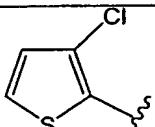
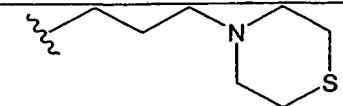
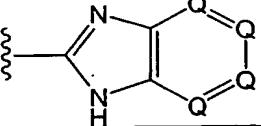
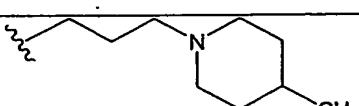
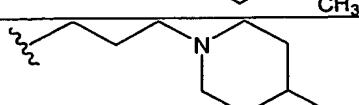
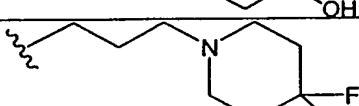
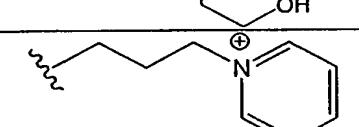
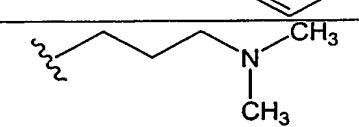
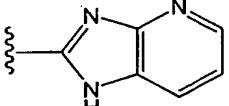
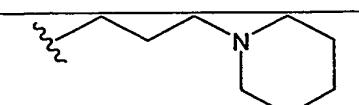
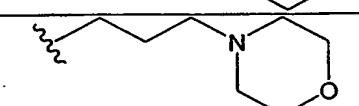
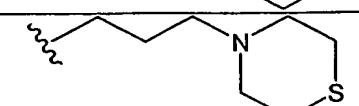
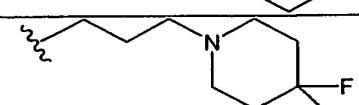
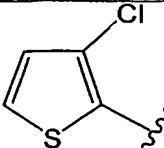
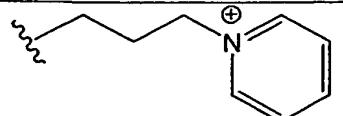
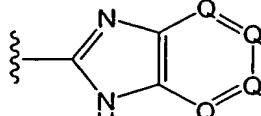
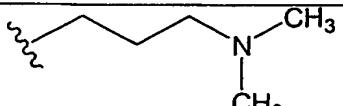
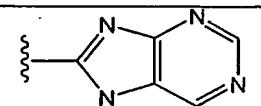
Ref. No.	$\text{Ar} - \text{wavy line}$	$\text{wavy line} - \text{R}^5$	$\text{wavy line} - \text{heterocyclic ring}$
A-51			
A-52	Same		Same
A-53	Same		Same
A-54	Same		Same
A-55	Same		Same
A-56	Same		Same
A-57	Same		
A-58	Same		Same
A-59	Same		Same
A-60	Same		Same
A-61	Same		Same

Table A (continued)

Ref. No.	Ar	$\text{---} \text{R}^5$	
A-62			
A-63	Same		

[0049] Compounds of this invention have been found to have anti-bacterial and/or anti-fungal properties and therefore may be used for preventing and/or treating infections in

5 eukaryotic organisms. For human anti-infective applications, an effective amount of a compound of this invention is used, optionally in combination with a pharmaceutically acceptable carrier. The composition may be dry, or it may be a solution. Treatment may be reactive, for combating an existing infection, or prophylactic, for preventing infection in an organism susceptible to infection. Preferably, compounds of this invention are used to treat 10 infections by drug-resistant strains of bacteria, for example MRSA (methicillin resistant *S. aureus*), MRSE (methicillin resistant *S. epidermidis*), PRSP (penicillin resistant *S. pneumoniae*) or VRE (vancomycin resistant *Enterococci*). By "drug-resistant" it is meant that the bacteria are resistant to treatment with conventional antibiotics.

[0050] Host organisms that can be treated include eukaryotic organisms, in particular plants 15 and animals. The plant may be an agriculturally important crop, such as wheat, rice, corn, soybean, sorghum, and alfalfa. Animals of interest include mammals such as bovines, canines, equines, felines, ovines, porcines, and primates (including humans). Accordingly, in another aspect of this invention, there is provided a method for treating a bacterial infection – particularly an infection by Gram-positive bacteria – comprising administering to a patient in 20 need of such treatment an effective amount of compound (I). Compounds of this invention can be used in the preparation of a medicament for treating a bacterial or fungal infection in a mammal. The compounds may be administered orally, topically, parenterally (e.g., intravenously, subcutaneously, intraperitoneally, transdermally) or by inhalation.

[0051] The practice of our invention can be further understood by reference to the following examples, which are provided by way of illustration and not of limitation.

Synthesis – General Remarks

[0052] Common abbreviations and acronyms are employed for various chemicals and

5 techniques, including: Boc for t-butylloxycarbonyl (and (Boc)₂O for the corresponding anhydride); DIEA for diisopropylethylamine; DMF for N,N-dimethylformamide; ESI-MS for electrospray ionization mass spectrometry; HBTU for 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; ¹H-NMR for proton NMR; MsCl for mesyl chloride; RP-HPLC for reverse phase high pressure liquid chromatography; RT for room
10 (ambient) temperature; TEA for triethylamine; and TLC for thin layer chromatography.

[0053] Typically, the structures of compounds were confirmed by ¹H-NMR and/or mass spectrometry. Where a parenthetical remark such as "¹H-NMR" or "mass spectrum" or "ESI-MS" follows a reference to a compound without any elaboration, it means that such spectrum was taken, was consistent with the assigned structure, and did not indicate the presence of
15 significant impurities.

[0054] The skilled artisan will understand that: (a) an intermediate described in the context of the synthesis of a particular compound of this invention can also be used to make other compounds of this invention, *mutatis mutandis*; (b) in certain experimental sections only the preparation of an intermediate compound is described, because its incorporation into a final
20 compound of this invention straightforwardly follows synthetic methodology described herein; and (c) for some reactions that recur herein, detailed reaction and work-up conditions sometimes are not provided in each instance in the interest of brevity and that the conditions described elsewhere in this application are adaptable to the instance at hand without undue experimentation.

25 Synthesis – General Procedures

[0055] The following general procedures are used frequently in the synthesis of compounds of this invention. This section describes each in detail. Subsequent recurrences are then simply referred to as "Procedure A," "Procedure B," etc.

Procedure A: Coupling of an aryl amine with an aryl acid

[0056] A mixture of the acid (1.2 eq.) and HBTU (1.15 eq.) in DMF/DIEA (3 eq, DIEA, ca. 3:1 DMF : DIEA by volume) was stirred at RT for 30 min. The amine (1.0 eq.) in DMF (ca. same volume) was added and the mixture stirred at RT for 2-16 hr. The mixture was added dropwise to ice-water containing 10% K₂CO₃ (ca. 40x reaction volume). The resulting precipitates were collected by filtration and dried. In cases where no precipitates formed, the solution was extracted with EtOAc (3x) and the combined organic phases were dried (MgSO₄) and concentrated. The resulting crude product was either used directly in the next step, or, in the case of a final product, purified by RP-HPLC (Hamilton PRP-1 column, CH₃CN/0.5% aq. AcOH, 0%, to 60% in 60 min). The purified product was characterized by 10 ¹H-NMR and ESI-MS.

Procedure B: Reduction of a nitro pyrrole to an amino pyrrole

[0057] A solution of the nitro pyrrole (1 eq.) in a solvent (typically EtOAc, MeOH, or DMF) was purged with nitrogen (N₂) gas for several minutes. Palladium on carbon (Pd/C) (0.05 eq. by weight) was added portion-wise while purging with N₂. The flask was sealed 15 and evacuated. Hydrogen gas (H₂) was introduced using a balloon. The evacuation was repeated several times, each time followed by the introduction of H₂. The reaction was stirred under a H₂ atmosphere for several hours until TLC analysis showed complete consumption of starting material. The flask was then purged with N₂ before opening. The Pd/C was removed by filtration through Celite© filter media. The solvent was either 20 removed to provide crude amino pyrrole (in the case of EtOAc and MeOH) or the solution of the product was used directly in the next step (in the case of DMF).

Procedure C: Saponification of an aryl ester to an aryl acid.

[0058] A mixture of the ester (1 eq.) and NaOH or KOH (ca. 0.5 g base per g ester) in water (ca. 1 g ester per 40 mL) and MeOH or EtOH (ca. 1 g ester per 20 mL) was stirred at 25 40-60 °C for 3-18 hr. The mixture was diluted with water (ca. 2x reaction volume), washed with HtOAc (1x) and acidified to pH 2-3 using ca. 6M aq. HCl. The resulting precipitates were collected by filtration and dried.

Procedure D: Mesylation of a primary alcohol and substitution with an amine

[0059] A mixture of the alcohol (1 eq.) and DIEA (3 eq.) in DMF (ca. 1 mL per 50 mg 30 alcohol) was treated with mesyl chloride (1.2 eq.) at RT then stirred for 1 hr at 40 °C. The amine (5~10 eq.) was added and the reaction mixture was stirred at 60 °C for 12 hr. After

cooling, the reaction mixture was diluted with 40% aq. AcOH and purified by RP-HPLC (Hamilton PRP-1 column, CH₃CN/0.5% aq. AcOH, 0% to 60% in 60 min). The purified product was characterized by ¹H-NMR and ESI-MS.

Synthesis – Specific Compounds

5 Example A

[0060] This example describes the synthesis of a subgenus of compounds (I) in which Ar is an isoquinoline group. The preparation of intermediate dimer acid 7 is shown in Fig. 1. Fig. 2 details the preparation of succeeding intermediate biaryl amines 21-24. The preparation of compounds A-1, A-12, A-13, and A-15 is outlined in Fig 3.

10 [0061] *Nitro pyrrole 3.* A mixture of pyrrole 1 (10.0 g, 54.3 mmol), alkyl chloride 2 (9.44 g, 1.1 eq.), NaI (8.14 g, 1 equiv.), and K₂CO₃ (16.51 g, 2 eq.) in DMF (150 mL) was stirred at 75 °C for 16 hr. After cooling, the mixture was poured into 1M HCl (500 mL) and washed with EtOAc (2 x 300 mL). Solid Na₂CO₃ was added carefully to neutralize the acid and the solution extracted with EtOAc (3 x 300 mL). The organic layers were dried (MgSO₄) and 15 evaporated to give nitro pyrrole 3 (7.77 g, 53%, ¹H-NMR).

20 [0062] *Amino pyrrole 4.* Nitro pyrrole 3 (7.65 g, 28.4 mmol) was reduced according to Procedure B in MeOH. Following removal of solvent, the crude dark brown oil product was taken up in EtOAc (200 mL) and MeOH (10 mL) and cooled in an ice bath. HCl gas was bubbled through the solution for ca. 30 sec. Evaporation of solvents gave amino pyrrole 4 (8.05 g, 91 %, yellow/brown solid, ¹H-NMR).

[0063] *Dimer ester 6.* Pyrrole 4 (1.2 g, 3.85 mmol) was coupled to isoquinoline carboxylic acid 5 (0.8 g) according to Procedure A to give dimer ester 6 (1.35 g, 90%, ¹H-NMR).

[0064] *Dimer acid 7.* Dimer ester 6 (1.30 g, 3.30 mmol) was saponified in NaOH/EtOH at 60 °C for 16 hr according to Procedure C, giving dimeric acid 7 (121 g, >95%, ¹H-NMR)

25 [0065] *Amides 13 to 16.* Amides 13 to 16 were prepared by coupling nitro pyrrole carboxylic acid 8 (2.71 g, 15.9 mmol) with diamines 9 to 12 (1.1 equiv), respectively, according to Procedure A (~70% average yield).

30 [0066] *Compounds 17 to 20.* Cyclization of amides 13 to 16 to compounds 17 to 20 was achieved by heating in acid. Compound 13 (16.05 g, 61.67 mmol) was heated at 60 °C in glacial AcOH (200 mL) for 2 hr. The AcOH was evaporated and Et₂O added to precipitate

product **17**, which was collected by filtration (7.82 g, 52%). Compound **14** (6.02 g, 23.1 mmol) was heated at reflux in glacial AcOH (200 mL) for 16 hr. Product **18** was collected in an analogous fashion to compound **17** (3.42 g, 61%). Compound **15** (7.31 g, 28.0 mmol) was heated at reflux in concentrated HCl for 16 hr. Evaporation of the solvent followed by addition of Et₂O caused precipitation of product **19** (4.0 g, 59%). Compound **16** (5.8 g, 22.0 mmol) was treated analogously to compound **14**, giving product **20** (2.74 g, 51 %).

[0067] *Amines 21 to 24.* Reduction of the nitro group in compounds **17** to **20** was carried out according to Procedure B in DMF to provide the corresponding amines **21** to **24**, which were used directly in the next step.

[0068] *Compounds A-1, A-12, A-13, and A-15.* Coupling of dimeric acid **7** (*ca.* 100 mg scale) with each of amines **21** to **24** was carried out according to Procedure A, providing the corresponding final products **A-1**, **A-12**, **A-13**, and **A-15**.

Example B

[0069] This example describes the synthesis of another subgenus of compounds (I) in which Ar is an isoquinoline group. The preparation of intermediate dimer acid **27** is shown in Fig. 4. Fig. 5 details the preparation of succeeding intermediate biaryl amines **37-39**. The preparation of compounds **A-2**, **A-3** and **A-4** is outlined in Fig. 6.

[0070] *Dimer ester 26* Amino pyrrole ester **25** (11.6 g, 68.97 turnoff was coupled to isoquinoline carboxylic acid **5** (14.3 g, 82.76 mmol) according to Procedure A to give dimer ester **26** (20.27 g, 91% ¹H-NMR).

[0071] *Dimer acid 27.* Saponification of ester **26** (19.5 g, 60.37 mmol) using NaOH in EtOH at 60 °C for 12 hr according to Procedure C gave dimer acid **27** (17.1 g, >95%, ¹H-NMR).

[0072] *Compounds 31 to 33.* Compounds **31** to **33** were prepared by coupling carboxylic acid **8** (1.0 g, 5.88 mmol) with diamines **28** to **30** (6.46 mmol, 1.1 equiv), respectively, according to Procedure A (~85% average yield).

[0073] *Compounds 34 to 36.* Cyclization of compounds **31** to **33** (5 mmol scale) was achieved by heating at 60 °C in glacial AcOH (100 ml.) for 2 hr to provide compounds **34** to **36**. The AcOH was evaporated and Et₂O added to precipitate the products, which were obtained by filtration and used without further purification (~60% average yield).

[0074] *Antines 37 to 39.* Reduction of the nitro group in compounds 34 to 36 was carried out according to Procedure B in DMF to provide corresponding amines 37 to 39, which were used directly in the next step.

[0075] *Compounds A-2, A-3 and A-4.* Coupling of dimeric acid 27 (ca. 100 mg scale) with amines 37 to 39 was carried out according to Procedure A, providing compounds A-2 to A-4.

5 *Example C*

[0076] This example describes the synthesis of yet another subgenus of compounds (I) in which Ar is an isoquinoline group. Fig. 7 details the preparation of trifluoroacetamido intermediate 45. The preparation of compounds A-5, A-8 and A-11 is outlined in Fig. 8.

10 [0077] *Compound 41.* Nitro-diamine 40 (1.0 g, 6.53 mmol) was dissolved in EtOH (2-5 mL) and DIEA (2.3 mL, 13.06 mmol) and the solution was cooled to 0 °C. Ethyl trifluoroacetate (0.93 g 6.53 mmol) was added and the reaction was stirred at 0 °C for 1 hr. The cooling bath was then removed and the reaction stirred at room temperature for 12 hr. The solution was poured into 10% aqueous K₂CO₃ solution and extracted with EtOAc (2x 100 mL). The organic layers were dried (MgSO₄) and evaporated to give compound 41 (¹H NMR) as a yellow oil, which was used directly in the next step without purification.

15 [0078] *Diamine 42.* The nitro group in compound 41 was reduced in EtOAC according to Procedure B. Following removal of the solvent, the crude dark brown oil product was taken up in EtOAc (25 mL) and cooled in an ice bath. HCl gas was bubbled through the solution for ca. 15 seconds. Addition of Et₂O caused precipitation of the dihydrochloride of diamine 42 (1.54 g, 81 % over 2 steps, oil-white solid, ¹H-NMR).

[0079] *Compound 43.* Coupling of carboxylic acid 8 (1.0 g, 5.88 mmol) with diamine 42 (1.5 g, 5.14 mmol) according to Procedure A gave compound 43 (1.04 g, 55%, ¹H-NMR).

20 [0080] *Compound 44.* Compound 43 (0.85 g, 2.3 mmol) was dissolved in glacial acetic acid (4 mL) and heated to 180 °C by microwave irradiation for 5 min. The solvent was evaporated to leave compound 44 (0.8 g, >95%, ¹H NMR), which was used without further purification.

25 [0081] *Trifluoroacetamido intermediate 45.* Reduction of the nitro group in compound 44 (0.5 g, 1.4 mmol) was carried out according to Procedure B in DMF to provide the trifluoroacetamido intermediate 45, which was used directly in the next step.

[0082] *Compound A-5.* Coupling of dimeric acid 27 (0.48 g, 1.62 mmol) with trifluoroacetamido intermediate 45 (1.4 mmol) in DMF according to Procedure A gave compound A-5.

[0083] *Compound A-8.* Compound A-5 (100 mg, 0.17 mmol) was dissolved in a mixture 5 of DMF (1 mL) and MeOH (2 mL). Solid K₂CO₃ (3 eq.) was added and the reaction mixture heated to 150 °C by microwave irradiation for 5 min. After cooling, the reaction mixture was diluted with 40% aqueous AcOH (to 15 mL total volume) and the product obtained by HPLC purification (Hamilton PRP-1 column, CH₃CN/0.5% aq. AcOH, 0% to 60% in 60 min).

[0084] *Compound A-11.* Compound A-8 (20 mg, 0.04 mmol) was dissolved in a mixture 10 of DMF (2 mL) and TEA (0.5 mL). The solution was cooled to 0 °C before addition of acryloyl chloride 46 (~10 mg). The reaction was stirred at 0 °C for 1 hr. Morpholine (47) was added arid the reaction stirred at room temperature for 2 hr. The reaction was diluted using 40% aqueous AcOH (to 15 mL total volume) and the product obtained by HPLC purification (Hamilton PRP-1 column, CH₃CN/0.5% aq. AcOH, 0% to 60% in 60 min).

15 *Example D*

[0085] This example describes the synthesis of yet another subgenus of compounds (I) in which Ar is an isoquinoline group. Fig. 9 details the preparation of intermediate hydroxy amine 52. The preparation of the final compounds A-6 and A-9 is outlined in Fig. 10.

[0086] *Diamine 49.* Reduction of the nitro group in nitro amine 48 (1.0 g 6.49 mmol) was 20 carried out according to Procedure B in DMF to provide a solution of diamine 49, which was used directly in the next step.

[0087] *Compound 51.* A mixture of diamine 49 (6.49 mmol) and aldehyde 50 (1.0 g, 6.49 mmol) in DMF (25 mL) was heated at 80 °C for 1 hr. Iron (III) chloride (0.21 g 1.30 mmol, 0.2 eq.) was added and the reaction heated at 120 °C for 12 hr in an open flask. After 25 cooling, the mixture was added dropwise to vigorously stirred ice-cold water, causing precipitation of compound 51, collected by filtration and dried (1.46 g, 87 %, ESI-MS, ¹H NMR).

[0088] *Hydroxy amine 52.* Reduction of the nitro group in compound 51 (0.25 g, 0.97 mmol) was carried out according to Procedure B in DMF to provide a solution of hydroxy 30 amine 52, which was used directly in the next step.

[0089] *Compound A-6.* Coupling of dimeric acid **27** (0.32 g, 1.10 mmol) with hydroxy amine **52** (0.97 mmol) in DMF according to Procedure A gave final product **A-6**.

[0090] *Compound A-9.* Compound **A-6** (25 mg, 0.05 mmol) was dissolved in a mixture of DMF (2 mL) and TEA (0.5 mL). The solution was cooled to 0 °C before addition of the acid chloride **46** (~10 mg). The reaction mixture was stirred at 0 °C for 1 hr. Morpholine **47** was added and the reaction stirred at RT for 2 hr. The reaction mixture was washed using 40% aq. AcOH (to 15 mL total volume) and compound **A-9** was isolated by HPLC purification (Hamilton PRP-1 column, CH₃CN/0.5% aq. AcOH, 0% to 60%, in 60 min).

Example E

10 [0091] This example describes the synthesis of yet another subgenus of compounds (I) in which Ar is an isoquinoline group. Fig. 11 details the preparation of morpholino intermediate **58**. The preparation of final compound **A-10** is outlined in Fig. 12.

15 [0092] *Phenol 53.* Aminophenol **48** (1.0 g, 6.49 mmol) was dissolved in DMF (10 mL) and DIEA (2.26 mL, 12.98 mmol). A Solution of (Boc)₂O (2.12 g, 9.73 mmol) in DMF (10 mL) was added dropwise at RT and the reaction left stirring for 16 hr. The mixture was added to vigorously stirred ice-cold water, causing precipitation of phenol **53**, which was collected by filtration and dried (yellow solid, 1.52 g, 92 %, ¹H NMR).

20 [0093] *Compound 55.* Solid NaOH (0.32 g, 7.8 mmol) was added to a solution of phenol **53** (1.0 g, 3.9 mmol) in DMF (10 mL) and the reaction mixture was stirred at RT for 1 hr. Alkyl chloride **54** (0.80 g, 4.29 mmol) was added and the reaction mixture was heated at 60 °C for 16 hr. The reaction mixture was poured into 10% aq. K₂CO₃ (100 mL) and extracted with EtOAc (2x 100 mL). The organic layers were dried (MgSO₄) and evaporated to give compound **55** (¹H NMR) as an oil, which was used directly in the next step without purification.

25 [0094] *Diamine 56.* Methanol (50 mL) was cooled to 0 °C and saturated with HCl (g). This solution was added to compound **55** (3.9 mmol) and the reaction stirred at RT for 1 hr. ESI-MS analysis showed complete removal of the Boc group. All volatile components were evaporated under high vacuum. The nitro group was then reduced according to Procedure B in DMF to provide a solution of diamine **56**, which was used directly in the next step.

30 [0095] *Compound 57.* A mixture of diamine **56** (3.9 mmol) and aldehyde **50** (0.6 g, 3.9 mmol) in DMF (15 mL) was heated at 80 °C for 1 hr. Iron (III) chloride (0.13 g, 0.78 mmol,

0.2 eq.) was added and the reaction heated at 120 °C for 12 hr in an open flask. After cooling, the mixture was added dropwise to a vigorously stirred solution of 10% Na₂CO₃ in ice-cold water, causing precipitation of compound 57, which was collected by filtration and dried (1.09 g, 75 %, ¹H NMR).

5 [0096] *Morpholino intermediate 58.* Reduction of the nitro group in compound 57 (0.1 g, 0.27 mmol) was carried out according to procedure B in DMF to provide a solution of morpholino intermediate 58, which was used directly in the next step.

10 [0097] *Compound A-10.* Coupling of dimeric acid 27 (0.091 g, 0.31 mmol) with morpholino intermediate 58 (0.27 mmol) in DMF according to Procedure A gave final product A-10.

Example F

[0098] This example describes the synthesis of yet another subgenus of compounds (I) in which Ar is an isoquinoline group. Fig. 13 details the preparation of intermediate trimer acid 60. The preparation of the final compound A-7 is outlined in Fig. 14.

15 [0099] *Trimer ester 59.* Pyrrole 25 (5.4 g, 32.14 mmol) was coupled to dimer acid 27 (10.90 g, 36.96 mmol) according to Procedure A to give Trimer ester 59 (12.17 g, 85%, ¹H-NMR).

20 [0100] *Trimer acid 60.* Saponification of trimer ester 59 (12.15 g, 27.32 mmol) using NaOH in EtOH at 60 °C for 12 hr according to Procedure C gave trimer acid 60 (10.94 g, >95%, ¹H-NMR).

[0101] *Compound 62.* Chloro diamine 61 (0.36 g, 2.54 mmol) was coupled to trimer acid 60 (1.0 g, 2.4 turmoil according to Procedure A to give compound 62 (0.88 g, 68%, ¹H-NMR).

25 [0102] *Compound A-7.* Compound 62 (0.21 g, 0.39 mmol) was dissolved in glacial AcOH (3 mL) and heated to 180 °C by microwave irradiation for 5 min. The solvent was evaporated and the residue diluted using 40% aq. AcOH (to 15 mL total volume) and compound A-7 obtained by HPLC purification (Hamilton PRP-1 column, CH₃CN/0.5% aq. AcOH, 0% to 60% in 60 min).

Example G

[0103] This example describes the synthesis of yet another subgenus of compounds (I) in which Ar is an isoquinoline group, as shown in Fig. 15 with reference to compound A-14.

5 [0104] *Compound A-14.* Dimeric acid 27 (0.20 g, 0.68 mmol) was coupled to amine 23 (0.145 g, 0.68 mmol) according to Procedure A, to give compound A-14.

Example H

10 [0105] This example describes the synthesis of a subgenus of compounds (I) in which Ar is a difluorobenzene group. The preparation of intermediate dimer acid 65 and its coupling with amines 21-24 in preparation of the final compounds A-16, A-17, A-18, and A-19 is outlined in Fig. 16.

[0106] *Dimer ester 64.* Pyrrole 4 (8.61 g, 27.56 mmol) was coupled to difluorobenzoic acid 63 (5.2 g) according to Procedure A to give dimer ester 64 (9.71 g, 93%, ¹H-NMR).

15 [0107] *Dimer acid 65.* Dimer ester 64 (9.70 g, 25.59 mmol) was saponified using NaOH in EtOH at 60 °C for 16 hr according to Procedure C, giving dimer acid 65 (1.21 g, >95%, ¹H-NMR).

[0108] *Compounds A-16, A-17, A-18 and A-19.* Coupling of dimer acid 65 (ca. 100 mg scale) with amines 21 to 24 was carried out according to Procedure A, providing respectively compounds A-16 to A-19.

Example I

20 [0109] This example describes the synthesis of a subgenus of compounds (I) in which Ar is a 4-chloro-2-fluorobenzene group. The preparation of intermediate dimer acid 68 and its coupling with amines 21-24 to prepare compounds A-31, A-39, A-45, and A-46 is outlined in Fig. 17.

25 [0110] *Dimer ester 67.* Pyrrole 4 (10.26 g, 32.84 mmol) was coupled to 4-chloro-2-fluorobenzoic acid 66 (6.9 g) according to Procedure A to give dimer ester 67 (11.31 g, 87%, ¹H-NMR).

[0111] *Dimer acid 68.* Dimer ester 67 (11.30 g, 28.57 mmol) was saponified using NaOH in EtOH at 60 °C for 16 hr according to Procedure C, giving dimer acid 68 (10.51 g, >95%, ¹H-NMR).

[0112] *Compounds A-31 A-39 A-45 and A-46.* Coupling of Compound 68 (*ca.* 100 mg scale) with amines 21 to 24 was carried out according to Procedure A, providing compounds A-31, A-39, A-45, and A-46.

Example J

5 [0113] This example describes the synthesis of a subgenus of compounds (I) in which Ar is a methoxyfluorobenzene or methoxychlorobenzene group. The preparation of intermediate dimer acids 69-70 and their coupling with amine 21 to yield compounds A-20 and A-21 is outlined in Fig. 18.

10 [0114] *Dimer acids 69 and 70.* Esters 64 (0.24 g, 0.63 mmol) and 67 (0.52 g, 1.36 mmol) were saponified and the 2-fluoro groups substituted by a methoxy group in one step, using NaOH in MeOH at 60 °C for 16 hr according to Procedure C, giving dimer acids 69 (0.22 g, >95%, ¹H-NMR) and 70 (0.46 g, 89%, ¹H-NMR) respectively.

15 [0115] *Compounds A-20 and A-21.* Coupling of dimer acids 69 and 70 (*ca.* 100 mg scale) with amine 21 was carried out according to procedure A, providing compounds A-20 and A21, respectively.

Example K

20 [0116] This example describes the synthesis of a subgenus of compounds (I) in which Ar is a chlorofluorobenzene group. The preparation of intermediate dimer acid 75 is shown in Fig. 19. Fig. 20 details the preparation of succeeding intermediate alcohol 76 and its conversion to compounds A-32 to A-38.

25 [0117] *Compound 72.* A mixture of pyrrole 1 (100 g, 0.54 mmol), 1-bromopropanol 71 (68.5 mL, 1.4 eq.), NaI (40.6 g, 0.5 eq.), and K₂CO₃ (150 g, 2 eq.) in DMF (1 L) was stirred at 75°C for 16 hr. After cooling, the mixture was poured into water (800 mL) and extracted with Et₂O (6x 200 mL). The organic layers were dried (MgSO₄) and evaporated to give compound 72 (109 g, 83%, ¹H-NMR) as an orange oil, which was used without further purification.

[0118] *Amino pyrrole 73.* Compound 72 (109 g, 0.45 mol) was reduced according to Procedure B in MeOH. Following removal of solvent, the crude dark brown oil product was taken up in EtOAc (500 mL) and MeOH (50 mL) and cooled in an ice bath. HCl gas was

bubbled through the solution for *ca.* 60 sec. Evaporation of the solvents gave amino pyrrole 73 (103 g, 92% $^1\text{H-NMR}$) as an off-white solid.

[0119] *Dimer ester 74.* Amino pyrrole 73 (40 g, 0.16 mol) was coupled to 4-chloro-2-fluorobenzoic acid (66) (28.1 g) according to Procedure A to give dialer ester 74 (46.0 g, 5 78%, $^1\text{H-NMR}$).

[0120] *Dimer acid 75.* Dimer ester 74 (46 g, 0.125 mol) was saponified using NaOH in EtOH at 60 °C for 16 hr according to Procedure C, giving dimer acid 75 (37.4g, 88%, $^1\text{H-NMR}$).

[0121] *Alcohol 76.* Amino pyrrole 21 (30.8 mmol, 1.5 eq.) was coupled to dimer acid 75 (7 10 g, 20.5 mmol) according to Procedure A to give intermediate alcohol 76 (4.5 g, 41%, $^1\text{H-NMR}$).

[0122] *Compound A-32.* Alcohol 76 (100 mg, 0.187 mmol) was mesylated and then heated with piperidine (10 eq.) according to Procedure D to give compound A-32 (25 mg 22%, $^1\text{H-NMR}$).

15 [0123] *Compounds A-33 to A-38.* Compounds A-33 to A-38 were made in analogy to compound A-32 by mesylation of alcohol 76 and subsequent treatment with the corresponding amine according to Procedure D.

Example L

[0124] This example describes the synthesis of yet another subgenus of compounds (I) in which Ar is a chlorofluorobenzene groups. Fig. 21 details the preparation of intermediate alcohol 77 and its conversion to compounds A-40 to A-44.

[0125] *Alcohol 77.* Amino pyrrole 22 (3.87 mmol, 1.2 eq.) was coupled to dimer acid 75 (1.1 g, 3.23 mmol) according to procedure A to give alcohol 77 (0.68 g, 39%, $^1\text{H-NMR}$).

[0126] *Compound A-40.* Alcohol 77 (88 mg, 0.164 mmol) was mesylated and then heated with morpholine (10 eq.) according to Procedure D to give compound A-40 (19 mg, 20%, $^1\text{H-NMR}$).

[0127] *Compounds A-41 to A-44.* These were made in analogy to compound A-40 by mesylation of alcohol 77 and then heating with the corresponding amine.

Example M

[0128] This example describes the synthesis of a subgenus of compounds (I) in which Ar is a 3-chlorobenzothiophene group. The preparation of intermediate dimer acid 80 and its coupling with amines 21-24 in preparation of compounds A-22, A-28, A-29, and A-30 is

5 outlined in Fig. 22.

[0129] *Dimer ester 79.* Amino pyrrole 4 (4.10 g, 13.14 mmol) was coupled to carboxylic acid 78 (3.4 g) according to Procedure A to give dimer ester 79 (536 g, 94%, ¹H-NMR).

[0130] *Dimer acid 80.* Dimer ester 79 (5.36 g, 12.35 mmol) was saponified using NaOH in EtOH at 60 °C for 16 hr according to Procedure C, giving dimer acid 80 (5.1 g, >95%, ¹H-

10 NMR).

[0131] *Compounds A-22 and A-28 to A-30.* Coupling of dimer acid 80 (ca. 100 mg scale) with amines 21 to 24 was carried out according to Procedure A, providing compounds A-22 and A-28 to A-30.

Example N

15 [0132] This example describes the synthesis of another subgenus of compounds (I) in which Ar is a 3-chlorobenzothiophene group. The preparation of intermediate dimer acid 82 is shown in Fig. 23, along with its transformation to intermediate alcohol 83 and the latter's conversion to compounds A-23, A-24, A-25, A-26 and A-27.

[0133] *Dimer ester 81.* Amino pyrrole 73 (35 g, 0.14 mol) was coupled to 3-

20 chlorobenzothiophene-2-carboxylic acid 78 (30.1 g) according to Procedure A to give dimer ester 81 (48.4 g, 85%, ¹H-NMR).

[0134] *Dimer acid 82.* Dimer ester 81 (48 g, 0.119 mol) was saponified using NaOH in EtOH at 60 °C for 16 hr according to Procedure C, giving dimer acid 82 (40.6 g, 90%, ¹H-NMR).

25 [0135] *Alcohol 83.* Amino pyrrole 21 (31.65 mmol, 1.5 eq.) was coupled to dimer acid 82 (8 g, 21.1 mmol) according to Procedure A to give alcohol 83 (3.02 g, 25%, ¹H-NMR).

[0136] *Compound A-26.* Alcohol 83 (70 mg, 0.122 mmol) was mesylated and then heated with morpholine (8 eq.) according to Procedure D to give compound A-26 (17 mg, 22%, ¹H-NMR).

[0137] *Compounds A-23-A-25 and A-27.* These compounds were made analogously to compound **A-26** from alcohol **83** and the corresponding amine or pyridine.

Example O

[0138] This example describes the synthesis of a subgenus of compounds (I) in which Ar is a 3-chlorothiophene group. The preparation of intermediate dimer acid **86**, its coupling with amines **21-22** and **24**, and the preparation of compounds **A-47**, **A-57** and **A-63** is outlined in Fig. 24.

[0139] *Dimer ester 85.* Pyrrole **4** (2.1 g, 6.73 mmol) was coupled to carboxylic acid **84** (1.31 g) according to Procedure A to give dimer ester **85** (2.12 g, 82%, ¹H-NMR).

[0140] *Dimer acid 86.* Dimer ester **85** (2.1 g, 5.52 mmol) was saponified using NaOH in EtOH at 60 °C for 12 hr according to Procedure C, giving dimer acid **86** (1.95 g, >95%, ¹H-NMR).

[0141] *Compounds A-47, A-57 and A-63.* Coupling of dimer acid **86** (ca. 100 mg scale) with amines **21**, **22** and **24** was carried out according to Procedure A, providing corresponding compounds **A-47**, **A-57**, and **A-63**.

Example P

[0142] This example describes the synthesis of another subgenus of compounds (I) in which Ar is a 3-chlorothiophene group. Fig. 25 shows the preparation of chlorothiophene-pyrrole dimer acid **88**, its transformation to compound **A-48**, and the latter's conversion to compounds **A-49** to **A-56**.

[0143] *Dimer ester 87.* Pyrrole **73** (40 g, 0.16 mol) was coupled to carboxylic acid **84** (26.2 g) according to Procedure A to give dimer ester **87** (44.5 g, 78%, ¹H-NMR).

[0144] *Dimer acid 88.* Dimer ester **87** (35.6 g, 0.10 mmol) was saponified using KOH in EtOH at 60 °C for 6 hr according to Procedure C, giving timer acid **88** (32.5 g, >95%, ¹H-NMR).

[0145] *Compound A-48.* Amine **21** (17.3 mmol, 1 eq.) was coupled to dimer acid **88** (5.68 g, 17.3 mmol) according to Procedure A to give compound **A-48** (3.01 g, 34%, ¹H-NMR).

[0146] *Compound A-51.* Compound A-48 (64 mg, 0.122 mmol) was mesylated and then heated with thiomorpholine (9 eq.) according to Procedure D to give compound A-51 (25 mg, 34%, ¹H-NMR).

[0147] *Compounds A-49 to A-50 and A-52 to A-56.* These compounds were made analogously to compound A-51 by the mesylation of alcohol A-48 and then heating with the corresponding amine or pyridine.

Example Q

[0148] This example describes the synthesis of yet another subgenus of compounds (I) in which Ar is a 3-chlorothiophene group. Fig. 26 details the preparation of intermediate alcohol 89 and its conversion to compounds A-58 to A-62.

[0149] *Alcohol 89.* Amino pyrrole 22 (17.84 mmol, 1 eq.) was coupled to acid 88 (5.87 g, 17.84 mmol) according to Procedure A to give alcohol 89 (2.71 g, 29%, ¹H-NMR).

[0150] *Compound A-59.* Alcohol 89 (50 mg, 0.095 mmol) was mesylated and then floated with morpholine (10 eq.) according to Procedure D to give compound A-59 (15 mg, 27%, ¹H-NMR).

Compounds A-58 and A-60 to A-62. These compounds were made analogously to compound A-59 from alcohol 89 and the corresponding amine or pyridine.

Biological Activity

[0151] *In vitro* biological activity data were collected for a variety of microorganisms, including *Bacillus cereus* (ATCC 11778), *Staphylococcus aureus* (ATCC 33591; ATCC 27660, a methicillin resistant strain (MRSA); ATCC 13709, a methicillin sensitive strain (MSSA)), *Enterococcus faecalis* (ATCC 29212), and *Streptococcus pneumoniae* (ATCC 49619). Additionally, antifungal activity data were collected for *Candida albicans* (ATCC 38247).

[0152] Compounds according to this invention were screened for their *in vitro* activities against selected species of bacteria and fungi. The minimal inhibition concentration (MIC) of these compounds was determined using the National Committee for Clinical Laboratory Standards (NCCLS) broth microdilution assay in microtiter plates, as set forth in: (1) the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS) Document M7-A4 (NCCLS, 1997); (2) the guidelines of the National Committee for Clinical Laboratory

Standards (NCCLS) Document M11-A4 (NCCLS, 1997); and (3) the guidelines and reference method of the National Committee for Clinical Laboratory Standards (NCCLS) Document M27-T (NCCLS, 1995). For antifungal assays, the method recommended in Murray, PR., 1995 Manual of Clinical Microbiology (ASM Press, Washington, DC.), was
 5 employed.

[0153] The results are presented in Table B below, which is keyed as follows:

Organism tested against:

A = *B. cereus* ATCC 11778

B = *C. albicans* ATCC 38247

C = *E. faecalis* ATCC 29212

D = *S. aureus* ATCC 13709

10 E = *S. aureus* ATCC 27660

F = *S. aureus* ATCC 33591

G = *S. pneumoniae* ATCC 49619

Activity:

+++ = MIC \leq 4 $\mu\text{g/mL}$

++ = 4 $<$ MIC $<$ 12 $\mu\text{g/mL}$

+ = 12 \leq MIC \leq 32 $\mu\text{g/mL}$

ND = not determined

15 >32 = preliminary data indicates MIC greater than 32 $\mu\text{g/mL}$

Table B
Biological Activity

Ref. No.	Organism (Minimum Inhibitory Concentration (MIC), $\mu\text{g/mL}$)						
	A	B	C	D	E	F	G
A-1	+++	+++	+++	+++	+++	+++	+++
A-2	+++	>32	+++	+++	+++	+++	+++
A-3	>32	>32	>32	>32	>32	>32	>32
A-4	+++	>32	+++	+++	+++	+++	+++
A-5	+++	>32	+++	+++	+++	+++	+++
A-6	+++	>32	+++	+++	+++	+++	+++
A-7	+++	>32	+++	+++	+++	+++	+++
A-8	++	>32	+++	+++	+++	+++	+++
A-9	+++	>32	+++	+++	+++	+++	+++
A-10	+++	>32	+++	+++	+++	+++	+++
A-11	+++	>32	+++	+++	+++	+++	+++

Table B
Biological Activity

Ref. No.	Organism (Minimum Inhibitory Concentration (MIC), $\mu\text{g/mL}$)						
	A	B	C	D	E	F	G
A-12	+++	>32	+++	+++	+++	+++	+++
A-13	+++	>32	+++	+++	+++	+++	+++
A-14	+++	>32	+++	+++	+++	+++	+++
A-15	+	>32	++	+	+	+	+++
A-16	+++	+	+++	+++	+++	+++	+++
A-17	+++	>32	+++	+++	+++	+++	+++
A-18	+	>32	+++	+	+++	+++	+++
A-19	+	>32	++	+	+	+	+++
A-20	+++	+	+++	+++	+++	ND	+++
A-21	+++	+	+++	++	+++	ND	+++
A-22	+++	+	++	++	++	ND	++
A-23	+++	+	+++	+++	+++	+++	+++
A-24	>32	>32	+++	+++	+++	+++	+++
A-25	>32	>32	+	+	+	+	++
A-26	+++	>32	+++	+++	+++	+++	+++
A-27	+	+	+	++	++	++	+
A-28	+++	>32	+++	+++	+++	+++	+++
A-29	+++	++	+++	+++	+++	+++	+++
A-30	+++	++	+++	+++	+++	+++	+++
A-31	+++	+	+++	+++	+++	+++	+++
A-32	+++	+	+++	+++	+++	+++	+++
A-33	+++	>32	+++	+++	+++	+++	+++
A-34	+++	+	+++	+++	+++	+++	+++
A-35	+++	>32	+++	+++	+++	+++	+++
A-36	++	+	+++	++	+++	+++	+++
A-37	+++	>32	+++	+++	+++	+++	+++
A-38	+++	+	+++	+++	+++	+++	+++
A-39	+++	+	+++	+++	+++	+++	+++
A-40	+++	>32	+++	+++	+++	+++	+++
A-41	+++	>32	+++	+++	+++	+++	+++

Table B
Biological Activity

Ref. No.	Organism (Minimum Inhibitory Concentration (MIC), $\mu\text{g/mL}$)						
	A	B	C	D	E	F	G
A-42	+++	+	+++	+++	+++	+++	+++
A-43	+++	>32	++	++	+++	++	+++
A-44	+	>32	++	++	+++	+++	+++
A-45	+++	++	+++	+++	+++	+++	+++
A-46	+++	>32	+++	+++	+++	+++	+++
A-47	+++	+	+++	+++	+++	+++	+++
A-48	+++	>32	+++	+++	+++	+++	+++
A-49	+++	+	+++	+++	+++	+++	+++
A-50	+++	>32	+++	+++	+++	+++	+++
A-51	+++	>32	+++	+++	+++	+++	+++
A-52	+++	+	+++	+++	+++	+++	+++
A-53	+++	+	++	+++	+++	+++	+++
A-54	+++	>32	+++	+++	+++	+++	+++
A-55	+	>32	+	+	++	++	++
A-56	>32	>32	>32	+	+	+	>32
A-57	++	>32	+++	+++	+++	+++	+++
A-58	+++	>32	+++	+++	+++	+++	+++
A-59	+++	>32	+++	+++	+++	+++	+++
A-60	+++	>32	+++	+++	+++	+++	+++
A-61	+++	>32	+++	+++	+++	+++	+++
A-62	>32	>32	>32	>32	+	+	+
A-63	>32	>32	+	+	+	+	+++

[0154] Additionally, some compounds were screened against *Enterococcus faecium* (ATCC 51559, a vancomycin resistant strain (VRE)), *Staphylococcus epidermidis* (ATCC 12228), *Streptococcus pneumoniae* (ATCC 51422, a penicillin resistant strain (PRSP)),

5 and/or *Streptococcus pyogenes* (ATCC 49399). These results are provided in Table C, keyed as follows:

Organism tested against:

A = *E. faecium* ATCC 51559B = *S. epidermidis* ATCC 12228C = *S. pneumoniae* ATCC 51422D = *S. pyogenes* ATCC 4399

Activity:

+++ = MIC \leq 4 $\mu\text{g}/\text{mL}$ ++ = 4 < MIC < 12 $\mu\text{g}/\text{mL}$ 5 + = 12 \leq MIC \leq 32 $\mu\text{g}/\text{mL}$ ND = not determined>32 = preliminary data indicates MIC greater than 32 $\mu\text{g}/\text{ml}$,

Table C
Additional Biological Data

Ref. No.	Organism (Minimum Inhibitory Concentration (MIC), $\mu\text{g}/\text{mL}$)						
	A	B	C	D	E	F	G
A-1	+++	+++	+++	+++	+++	+++	+++
A-2	+++	+++	+++	+++	+++	+++	+++
A-4	+++	+++	+++	+++	+++	+++	+++
A-5	+++	+++	+++	+++	+++	+++	+++
A-7	+++	+++	+++	+++	+++	+++	+++
A-16	+++	+++	+++	+++	+++	+++	ND
A-43	+++	+++	++	++	+++	++	+++
A-45	+++	+++	+++	+++	+++	+++	+++
A-48	+++	+++	+++	+++	+++	+++	+++
A-49	+++	+++	+++	+++	+++	+++	+++
A-50	+++	+++	+++	+++	+++	+++	+++
A-51	+++	+++	+++	+++	+++	+++	+++
A-54	+++	+++	+++	+++	+++	+++	+++

[0155] Preferably, compounds of this invention have an MIC of 4 or less against at least

10 one strain of drug resistant bacteria, such as *Staphylococcus aureus* (ATCC 27660), *Streptococcus pneumoniae* (ATCC 51422), and *Enterococcus faecium* (ATCC 51559).

[0156] The foregoing detailed description of the invention includes passages that are chiefly or exclusively concerned with particular parts or aspects of the invention. It is to be understood that this is for clarity and convenience, that a particular feature may be relevant in

more than just the passage in which it is disclosed, and that the disclosure herein includes all the appropriate combinations of information found in the different passages. Similarly, although the various figures and descriptions herein relate to specific embodiments of the invention, it is to be understood that where a specific feature is disclosed in the context of a 5 particular figure or embodiment, such feature can also be used, to the extent appropriate, in the context of another figure or embodiment, in combination with another feature, or in the invention in general.

- [0157] Further, while the present invention has been particularly described in terms of certain preferred embodiments, the invention is not limited to such preferred embodiments.
10 Rather, the scope of the invention is defined by the appended claims.